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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,162	09/22/2003	Ronald R. Breaker	25006.0016U2	4368

23859 7590 12/22/2006
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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,162	BREAKER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *8-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Non-compliance Notice*.

DETAILED ACTION

This Office action is in response to the communication filed 10-23-06.

Claims 1-18 are pending in the instant application.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **Please provide SEQ ID Nos. for the sequences disclosed in the figures and text of the instant specification (see e.g., figures 1, 6, 9, 10, 12-15, 18, 19, 22-24, 28, 30, 32-35, 40-46).** See the accompanying Notice to Comply.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-7, guanine-responsive riboswitches, in the reply filed on 10-23-06 is acknowledged. The traversal is on the ground(s) that no serious burden would exist to examine all of the different riboswitches claimed, including but not limited to guanine, adenine, lysine, thiamine, and S-adenosylmethionine-responsive switches. This is not found persuasive because the different riboswitches are structurally, biologically and chemically distinct and one does

not render the other obvious. Furthermore, the searches required for proper examination of all of these compounds, and methods of using and methods of identifying all of the different riboswitches would not be coextensive, although they might be overlapping. And, contrary to Applicant's assertions, the searches required for proper examination of all of the different inventions claimed would require burdensome searches of the patent and non-patent data bases.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10-23-06.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to regulatable gene expression constructs comprising nucleic acid molecules encoding an RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule.

The specification and claims do not adequately describe the very broad genus comprising regulatable gene expression constructs comprising riboswitches that are activated by a trigger molecule and produce a signal upon activation, and which constructs further comprise a control strand, an aptamer domain, and an expression platform domain comprising a regulated strand. This very broad genus encompasses a vast array of molecules and combination of subunits or component parts, and the disclosure fails to provide a representative number of species for the very broad genus which provide for the functions claimed, of regulating expression of a nucleic acid strand, and which riboswitches produce a signal upon activation by a trigger molecule..

The specification and claims do not adequately describe the concise structural features (e.g. polynucleotide sequences, structures of all component parts of the gene expression constructs) that distinguish structures within the broadly claimed genus from those without. The specification teaches the 5'-UTR of the *B. subtilis* xpt-pbuX mRNA

as a potential guanine-specific riboswitch (figures 24-26 of the instant specification). The specification also teaches a comparison between this 5'-UTR fragment (of 185 nucleotides) and other bacterial sequences, whereby a purportedly conserved RNA motif, termed a "G box" has been identified as domain for a guanine-riboswitch, suggesting that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required, yet undefined three-dimensional fold necessary for riboswitch function (see e.g. p. 139 of the instant specification). The specification also discusses the ability of hypoxanthine, xanthine and adenine to also effect target nucleic acid cleavage under various conditions with this 5'-UTR fragment.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species, requisite sequences, structural components, or higher order structures to describe the genus comprising RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule. The description provided in the instant disclosure does not adequately describe the elements, structures or sequences required for the broad genus claimed.

Thus, one of skill in the art would reasonably conclude that Applicant was not in possession of the broadly claimed genus.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of searching for candidates of the genus comprising RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule, does not reasonably provide enablement for predictably making and designing the members of the broad genus of molecules claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to regulatable gene expression constructs comprising nucleic acid molecules encoding an RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a

regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The art teaches various allosteric mechanisms that certain mRNAs reportedly use to regulate gene expression in response to various metabolites, including thiamine pyrophosphate and lysine respondent mechanisms that affect thiamine and lysine biosynthetic processes respectively. .

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of making and using a representative number of species of regulatable gene expression constructs comprising nucleic acid molecules encoding RNA comprising riboswitches operably linked to coding regions, which riboswitches are adequately described and found to predictably regulate expression of the RNA.

The specification teaches the identification of a 5'-UTR fragment of the *B. subtilis* xpt-pbuX mRNA as a potential guanine-specific riboswitch (figures 24-26 of the instant specification). The specification also teaches a comparison between this 5'-UTR

fragment (of 185 nucleotides) and other bacterial sequences, whereby a purportedly conserved RNA motif, termed a "G box" has been identified as a domain for a guanine-riboswitch, suggesting that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required three-dimensional fold necessary for riboswitch function (see e.g. p. 139 of the instant specification).

The ability to test various sequences for their ability to cleave target nucleic acid strands in the presence of various ligands, and the postulation of required, yet undefined higher order structural constraints for riboswitch activities, however, is not representative of the ability to predictably make and use the broad genus of compounds claimed. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with determining the necessary sequence and structural components for designing functional riboswitches.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to regulatable gene expression constructs comprising nucleic acid molecules encoding an RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of sequence and structural characteristics, based on the identification and characterization of a representative number of species of the genus of compounds claimed, whereby riboswitches are identified, designed and constructed without undue experimentation. Since the specification fails to provide sufficient guidance for the successful design of the broad genus of riboswitches claimed, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Breaker.

Breaker (Curr. Opin. Biotech., 13: 31-39, Feb. 1, 2002) teaches a gene expression construct comprising a riboswitch, derived from either a naturally occurring or a non-naturally occurring riboswitch, operably linked to a coding region, which riboswitch comprises an aptamer domain and an expression platform domain, which aptamer domain comprises a P1 stem, which P1 stem comprises an aptamer strand and a heterologous control strand, and the expression platform comprises a regulated strand, and which regulated or control strand forms a stem structure, and which

riboswitch produces a signal when activated by a guanine trigger molecule (see the text on p. 31; fig. 2 on p. 33; fig. 3 on p. 34; text on p. 38).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
12-17-06

J Zara TC1600

JANE ZARA, PH.D.
EXAMINER

Application No.: 10/669,162

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: PLEASE PROVIDE ACCOMPANYING SEQ ID NOS. FOR SEQUENCES DISCLOSED IN SPEC + FIGURES (eg FIS 1, 6, 9, 10, 12-15, 18, 19, 22-24, 28, 30...)

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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